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Generation of activity–rest patterns by dual circadian pacemaker systems: a model

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SUMMARY Activity–rest patterns displayed by an animal under various circumstances are suggested to result from the combined influences of two virtually identical circadian pacemaker components. Increased output of each component proportionally increases the probability of activity of the animal. Such a dual circadian pacemaker model explains much of the phenomenology of activity–rest records. Under normal light–dark schedules, the two components of the model have a similar phase relationship to the Zeitgeber. Differential synchronization of the components to dawn and dusk is not assumed.

KEYWORDS circadian pacemaker, model, rest–activity pattern, simulations, splitting

INTRODUCTION

When nocturnal mammals are kept in constant bright light, or when diurnal mammals are kept in constant darkness, some individuals gradually redistribute their activity such that it shows a periodicity of about 12 h instead of 24 h. This phenomenon, called splitting, is of interest because it may limit the number of possible models of the circadian pacemaker. Pittendrigh and Daan (1976) suggested a model of differential responsiveness to light of two oscillators. One of the oscillators would synchronize to dawn (morning oscillator, M) the other to dusk (evening oscillator, E). During splitting, as well as in the case of a normal circadian activity pattern, activity was considered to result from the added influences of the two oscillators. The oscillators influence each other by mutual phase control. Pittendrigh and Daan (1976) suggested that the two oscillators enable an organism to adjust to changes in the photoperiod.

The model, analysed by Daan and Berde (1978), proved to be sufficient to describe many of the phenomena that occur during splitting and during normal circadian periodicity, as well as during the transitions between these states. They showed that light could cause splitting by influencing the coupling as well as by differentially modifying the frequency of the two oscillators. They further found that the two oscillators had to be nearly identical in order to show two stable phase relationships (in phase and 180° out of phase) as observed in splitting hysteresis. Daan and Berde (1978) therefore suggested as an alternative that bilateral symmetry rather than two functionally different oscillators might be involved. Subsequently, experimental unilateral SCN destruction in hamsters led to the abolition of splitting (Pickard and Turek 1985), while exposure to continuous light of hamsters with incomplete unilateral lesions caused a reduced incidence of splitting, usually with the clear dominance of one of the two components (Davis and Gorski 1984). Zlomanczuk *et al.* (1991) recently showed that the split pattern in *Phodopus sungorus* is reflected in two 180° out-of-phase peaks in the electrical activity of the SCN, in brain slices. Both peaks were observed in both the left and right SCN (which remained connected in the preparation). This suggests strongly that the split is generated at the pacemaker level, although the evidence for left and right association of the two components is still inconclusive.

Apart from the neurophysiological evidence against a functional differentiation in the dual pacemaker system, the behavioural patterns also argue against it. In hamsters, where splitting had been studied originally, the circadian activity pattern is distinctly unimodal. In *Tupaja belangeri,* dawn and dusk peaks are occasionally seen (Meijer *et al.* 1990), but during splitting, these peaks do not change their temporal relationship. Instead, splitting seems to develop from the gradual divergence in time of two similar activity profiles. Furthermore, the two components in *Tupaja* showed indistinguishable phase responsiveness to light pulses (Meijer *et al.* 1990), just as do the two components in hamsters to dark pulses (Boulos and Rusak 1982).

For these reasons we favour presently the interpretation that splitting in rodents reflects a change in the relationship (due to the altered coupling in constant light conditions) between two similar pacemakers (probably bilaterally distributed) rather than being due to two functionally

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distinct oscillators. It is worthwhile exploring the splitting phenomenon in some more detail, since it may inform us about the control over activity and rest exerted by each of the two pacemakers independently and in interaction.

In the transitional phase between the unsplit and the split state, a simple addition of the influences of the two underlying oscillators is not sufficient to explain the activity pattern. Some records (Meijer *et al.* 1990) clearly show almost complete suppression of activity at times when only one of the two oscillations reaches low values. We therefore propose to modify the E–M oscillator model; not the mechanism which causes splitting by light to affect either frequency or coupling, but rather the output of the model system by which activity is generated.

SPLITTING ACTIVITY PATTERNS

Even in conditions of constant light or constant darkness some animals do show pronounced activity peaks near subjective dawn and subjective dusk (Aschoff 1966). Since the E–M oscillator model consists of two oscillators, one thought to be synchronized to dawn, the other to dusk, it was natural to propose that the two peaks result from the two underlying oscillators (Pittendrigh and Daan, 1976). If this were true, one would expect that the activity peaks would change their mutual phase relationship during the transition to the split state. In *Tupaja,* however, the entire activity pattern seems to shift with respect to a copy image (Fig. 2). Obviously, such observations suggest that both underlying oscillators generate identical patterns P_1 and P_2.

TIMES OF REDUCED ACTIVITY

During the transition between the unsplit and the split state, the gradual drift apart of the patterns P_1 and P_2 can be observed. If the two contributions simply added up to yield the final activity pattern, one would expect to find some activity at all moments when at least one of the contributions is positive. This does not seem to be the case. Some records show nearly full suppression of activity at times where only one of the two contributions is close to zero. Hence, a simple addition of the influences of the underlying oscillators is insufficient to explain the results. From the many alternatives, the multiplication of influences is a simple and convenient possibility.

PROBABILITY OF ACTIVITY

Multiplication is appealing if one considers the influences of the separate oscillators in terms of probabilities. Depending on the particular behavioural aspect which is monitored, and on the sensitivity of measurement technique, each record shows more or less fragmentation of activity. Analysing the records at the same circadian phase over a series of days, yields a certain percentage of days when activity is observed. This fraction estimates the probability of finding activity at that circadian phase. If both oscillators have their own stochastic influence on the incidence of activity, it is logical to multiply the respective probability functions. The probability of a result based on the simultaneous occurrence of independent stochastically determined events is found by multiplication of the probabilities of the occurrence of these events.

SIMULATIONS

In order to be able to simulate activity records on the basis of the modified dual oscillator model, one needs to know the two individual probability functions P_1 and P_2. The shapes of these functions can be derived from records in which the phase angle, ψ, between the two components varies over a full cycle. For that purpose, a series of days has to be selected from the record, for which ψ increases in equal steps from zero to 360 degrees. Figure 1 shows an example from the record of Fig. 2, for which the step-size is 18 degrees, or 1/20th of a cycle. It is easily shown mathematically that the shape of the probability functions can be derived from the figure by calculating the fraction of days showing activity at each phase, φ, in two ways. For P_1 φ is defined with respect to activity onset of component 1; for P_2 φ is defined with respect to component 2. It is obvious from Fig. 1 that the shapes of P_1 and P_2 are very similar. They can be described by a more or less constant value in the activity phase, and a gradual increase from almost zero in the rest phase. Although there are insufficient data to specify the process, we surmise that this slow increase is somehow related to a homeostatic conservation of rest, which appears to be a general phenomenon across the animal kingdom (Tobler 1985). Under the assumption that the contributions P_1 and P_2 are identical, values can be chosen for the slope of the ramp function and the level of the square function, and simulations can be performed. For each time interval of the simulation the phase angles of P_1 and P_2 are taken from the record and the corresponding probabilities are multiplied. If the result exceeds a number chosen at random from a uniform distribution with limits 0 and 1, then activity is indicated in the plot. The results of such simulations are visualized in Figs 2 and 3. In Fig. 2 this concerns a record from *Tupaja belangeri* (Meijer *et al.* 1990). The animal did not show any stable coupling of the two components for an unusually long period of time. Similarly, a simulation of data on splitting in a *Tupaja* (Hoffmann 1971) is presented in Fig. 3. The examples clearly show how the probability profiles lead to the sharp and precise activity cut-offs and blurred activity onsets, as often observed in splitting (Meijer *et al.* 1990).

DISCUSSION

The examples in Figs 2 and 3 show that the proposed modifications of the E–M oscillator model lead to realistic simulations. Fine adjustments of the probability functions P_1

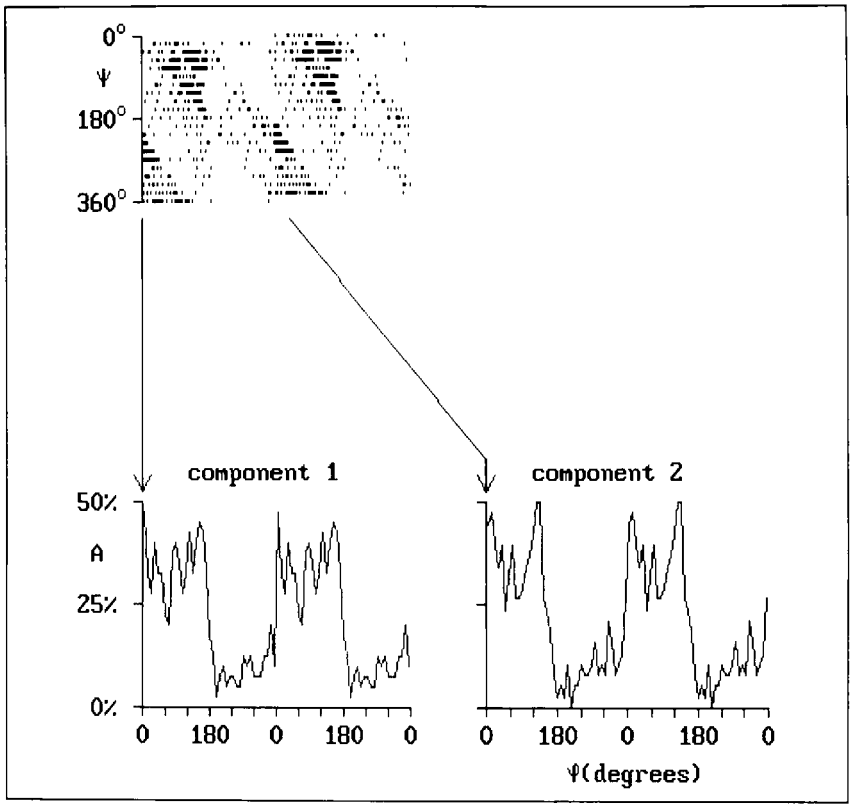

Figure 1. Top panel: Double plot of twenty individually selected days from an activity record of a *Tupaja belangeri,* selected such that the phase difference, ψ, between the components increases in steps of 1/20th of a cycle. Lower panels: For each phase angle, φ (varied in steps of 1/100th of a cycle), the fraction of days is counted when activity occurred at that phase (A). In the lower left panel φ is defined relative to activity onset of component 1, in the lower right panel relative to activity onset of component 2. Arrows are aligned along $\varphi = 0$ for the two components. They indicate the direction of projection of the top figure in order to obtain the individual components in the lower panels.

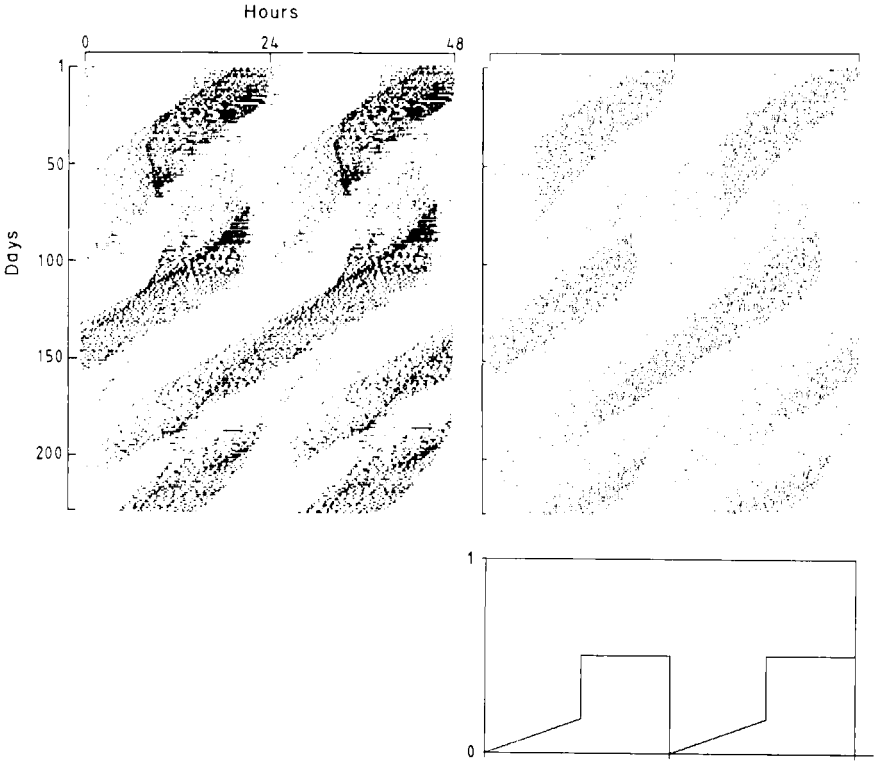

Figure 2. Left panel. Activity record of *Tupaja belangeri* (from Meijer *et al.*, 1990; fig 9). Right panel: simulation based on observed phase angles of the two components. The shapes of the two activity probability functions (plotted in the lower panel) are simplifications of the functions obtained in Fig. 1, and assumed to be identical. Simulations are performed per 5 min interval, corresponding to the temporal resolution of the data.

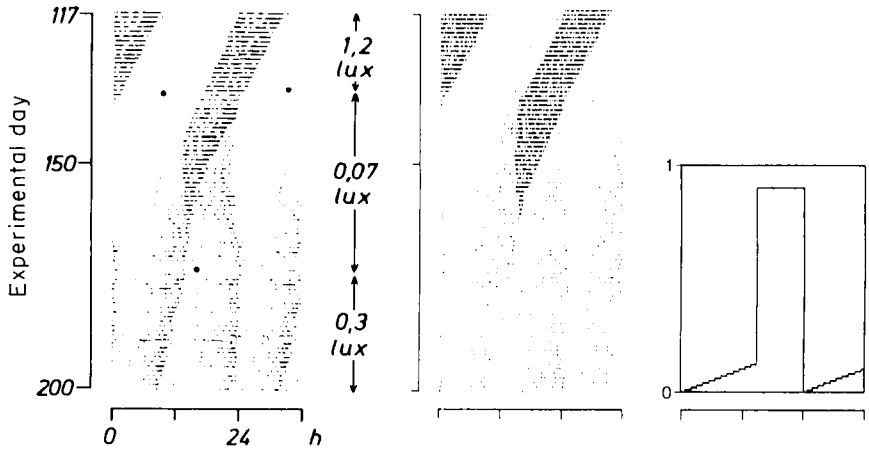

Figure 3. Left panel. Splitting in *Tupaja belangeri* (from Hoffmann, 1971; fig. 1). Right panel: simulation based on observed phase angles of the two components. The shapes of the two activity probability functions (plotted in the right panel) are assumed to be identical. Parameter values are estimated from Hoffmann's data. Simulations are performed per 10 min interval.

and P_2 will further improve the similarity between data and simulations. An important aspect to the quality of the similarities is the linear trend in the probability function for the 'rest'-half of the cycle. This trend generates the intervals of suppressed activity shortly after termination of each of the activity episodes. By taking this approach, we implicitly attribute this phenomenon of suppressed activity to the oscillators. It is also conceivable that the prior activity in itself is the origin of the suppressed activity, by generating a need for sleep or rest. Such homeostatic regulation can largely be independent from the circadian pacemaker, as has been discussed in the context of the two-process model of sleep regulation (Daan *et al.* 1984). Some details in the records suggest that part of the phenomenon must be attributed to the pacemaker itself. However, a homeostatic component can, as yet, not be excluded.

In the present modifications of the E–M oscillator model the basic mechanism of coupling is not altered. Only the translation of the output of the model in terms of observable activity is modified. Yet, the modification has considerable consequences for a functional interpretation. The present view does not distinguish an E and an M oscillator. Instead, two identical oscillators are involved, which, under normal circumstances are in phase. In accordance with the observations of Meijer *et al.* (1990), the functions describing the reactions of these oscillators to light pulses are identical. Adaptations to changes in the photoperiod are therefore no longer thought to result from a changing phase relationship between the two oscillators. When the two oscillators are found to be in phase under conditions of normal circadian periodicity in constant light, they definitely will be in phase when the light–dark transitions exert similar stabilizing influences via the similar PRC's. Hence, each of the two activity profiles and, hence, each of the two oscillators, must somehow adapt to changes in photoperiod.

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